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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,192	10/15/2001	Avi J. Ashkenazi	GNE.2630P1C9	3437

7590 03/01/2007

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
03/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/978,192	**Applicant(s)** ASHKENAZI ET AL.	
	Examiner Eileen B. O'Hara	**Art Unit** 1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 01 February 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: 58-62.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 11. does NOT place the application in condition for allowance because: In the response filed February 1, 2007, Applicants assert that the gene amplification data disclosed in Example 114 establishes a credible, substantial and specific patentable utility for the PRO274 polypeptide and the claimed antibodies that bind it as a diagnostic marker of lung tumors. At page 3 of the response, Applicants discuss Gygi et al., and submit that Gygi clearly indicates that high levels of mRNA generally correlate with high levels of protein. However, as a first point, Godbout et al. clearly teaches that in general, amplified genes do not have increased transcription into mRNA, and additionally, there is no evidence that the PRO274 mRNA is present at higher levels in lung tumors compared to normal lung tissue.

Applicants discuss the Futcher et al. reference, which demonstrates a good correlation between mRNA and protein levels. However, as discussed previously, although Futcher et al. demonstrates a correlation between mRNA abundance and protein abundance, there are numerous other articles which demonstrate that there is not a correlation between mRNA and protein levels.

Applicants on page 5 of the response submit that the utility standard is not absolute certainty, and that to overcome the presumption of truth that an assertion of utility by an applicants enjoys, the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility, and therefore, Applicants do not need to establish that transcription initiation is the only means of regulating gene expression in order to meet the utility standard. Applicants submit that as long as transcription initiation is the most common point of regulation, as admitted by the Examiner, it would be more likely than not that a change of the transcription level of a gene gives rise to a change in translation level of a gene.

Applicants on page 6 of the response assert that the submitted references, which represent experiments conducted by a large number of different research groups, demonstrate a trend of correlation found across proteins in general, and that this trend is confirmed by an overwhelming number of experiments by different researchers, using diverse experimental designs, testing various types of tissues, under numerous biological conditions. Although only a single gene or a small group of genes was tested by each individual study group, the cumulative evidence generated by over one hundred study groups certainly establishes that it is well-accepted in the art that a general mRNA/protein correlation exists. Applicants discuss Alberts and Lewin as support for transcriptional controls are the most important for protein levels. However, as discussed in the previous office action, Alberts also teaches that there are a number of other controls that can act later in the pathway from RNA to protein to modulate the amount of protein that is made, including translational control mechanisms and mRNA degradation control mechanisms (see Alberts 3rd ed., bottom of pg 453).

At page 6 of the response, Applicants submit that Meric et al. simply summarizes the translational regulation of cancer cells. Applicants submit that Meric indicates that translation initiation is regulated in response to nutrient availability and mitogenic stimulation and is coupled to cell cycle progression and cell growth, and that Meric never suggests that the translation of a cancer gene is suppressed in cancer in general, and that therefore, increased mRNA levels will not, in general, yield increased protein levels. It is submitted that Meric teaches that the translation efficiency of a number of cancer genes is enhanced in cancer cells compared to their normal counterparts (for instance, in patients with multiple myeloma, a C-T mutation in the c-myc IRES was identified and found to cause an enhanced initiation of translation (page 974, column 1)), and that therefore the level of proteins encoded by these genes increases in cancer cells at an even higher magnitude than the corresponding mRNA level. Applicants assert that Meric clearly supports Applicants' assertions that it is more likely than not that, in general, changes in mRNA levels are correlated with changes in protein levels.

Regarding the teachings of Meric, that the translation efficiency of a number of cancer genes is enhanced in cancer cells compared to its normal counterpart due to mutation, the PRO274 mRNA has not be demonstrated to be a cancer gene, that is, involved in any aspect of cancer, unlike the cancer genes discussed in Meric, and additionally, the specification does not teach that PRO274 mRNA in cancer cells have a mutation that would lead to increased translation. On page 973, Meric dissusses the three main alterations at the translational level that that can occur in cancer:

"Three main alterations at the translational level occur in cancer: variations in mRNA sequences that increase or decrease translational efficiency, changes in the expression or availability of components of the translational machinery, and activation of translation through aberrantly activated signal transduction pathways. The first alteration affects the translation of an individual mRNA that may play a role in carcinogenesis. The second and third alterations can lead to more global changes, such as an increase in the overall rate of protein synthesis, and the translational activation of several mRNA species."

Applicants have not demonstrated that in the cancer cells expressing PRO274 mRNA, any such alterations leading to global changes that would increase the overall rate of protein synthesis have occurred, such that one of ordinary skill in the art would expect PRO274 protein to be increased.

Applicants address the arguments made in the previous office action that the majority of references cited by Applicants drawn to genes known or suspected to be over expressed or under expressed in cancers, and that are involved with cell proliferation, differentiation and/or cell adhesion/migration, in which expression of the protein is important in the development and progression of the cancer. Applicants submit that, in fact, a number of the references submitted with Applicants' IDS filed August 3, 2006, are drawn to proteins that are not members of the above protein categories and have no obvious association with cancer, Rudlowski et al. examined the expression of glucose transporters 1-4; Papotti et al. studied three somatostatin receptors; Van der Wilt et al. studied deoxycytidine kinase; and Grenback et al. studied galanin. Applicants' arguments have been fully considered but are not deemed persuasive. As discussed previously, even with proteins not know to be involved in cancer, while some references demonstrate a correlation between a specific mRNA and level of the encoded protein, some do not.

Applicants starting at page 7 of the response assert that the more recent references by Orntoft et al., Hyman et al. and Pollack et al. more accurately reflect the state of the art regarding the correlation between gene amplification and transcript expression than the references cited by Godbout et al. Upon consideration, these references are convincing that gene amplification generally results in increased transcription.

Applicants discuss Li et al., which considered genes amplified if they had a copy number ration of at least 1.40, while an appropriate threshold for considering a gene amplified is a copy number of at least 2.0 (PRO274 is 2.0 to 3.05-fold amplified). This argument is persuasive.

At page 9 of the response Applicants discuss the Nagaraja et al. reference, and submit that the fact that many more transcripts than proteins were found to be differentially expressed does not mean that most mRNA changes did not result in correlating protein

changes, but merely reflects the fact that expression levels were only measured at all for many fewer proteins than transcripts

Applicant's arguments have been fully considered but are not found to be persuasive. Nagaraja et al. characterize comprehensive transcript and proteomic profiles of cell lines corresponding to normal breast (MCF10A), noninvasive breast cancer (MCF7) and invasive breast cancer (MDS-MB-231 and report that "the proteomic profiles indicated altered abundance of fewer proteins as compared to transcript profiles" (see abstract), and "the comparison of transcript profiles with proteomic profiles demonstrated that altered proteins were not always represented in the microarray designated profiles and vice versa" (see pg 2329, first column). The variability between the transcript profiles (mRNA) and proteomic profiles of Nagaraja et al. simply provide evidence that one skilled in the art would not assume that an increase in mRNA expression would correlate with significantly increased polypeptide levels. Applicant is holding Nagaraja et al. to a higher standard than their own specification, which does not examine corresponding protein levels for the PRO genes that purportedly displayed mRNA overexpression.

At pages 9-10 of the Response, Applicant argues that Waghray et al. (cited by Examiner in the previous Office Action) did not take genes which showed significant mRNA changes and check the corresponding protein levels, but looked at a small and unrepresentative number of proteins and checked the corresponding mRNA levels, and that Waghray et al. does not teach that changes in mRNA expression were not correlated with changes in expression of the corresponding protein. Applicants arguments are persuasive and this reference is not relevant.

At pages 10-11 of the Response, Applicant asserts that Sagynaliev et al. drew conclusions based upon a literature survey of gene expression data published in human CRC and not from experimental data. Applicants submit that the number of mRNAs examined in transcriptomics studies is typically much larger than the number of proteins examined in corresponding proteomics studies, due to difficulties in detecting and resolving proteins, and that it is well known in the art that there are problems associated with selecting only those proteins detectable by 2D gels.

Applicant's arguments have been fully considered but are not found to be persuasive. Sagynaliev et al. attempt to construct a gene expression "data warehouse" for human colorectal cancer (CRC) by performing a literature survey of gene expression data. Although Sagynaliev et al. do not experimentally examine mRNA and protein expression, they do state that correlation between results of transcriptomics versus proteomics results is low (page 3077, bottom of col 1). Sagynaliev et al. also make the point that "...many genes and factors found to be differentially regulated (both in transcriptomics and proteomics studies) do not play a casual role in CRC carcinogenesis" (pg 3077, col 2, 1st paragraph). Sagynaliev et al. was simply cited by the Examiner to emphasize the unpredictability in the art of correlating mRNA levels to protein levels.

Applicants on page 11 of the response assert that The Patent Office has failed to meet its initial burden of proof that Applicant's claims of utility are not substantial or credible. The arguments presented by the Examiner in combination with the previously cited Pennica et al. and Gygi et al. papers, as well as the newly cited Li, Nagaraja, Waghray, and Sagynaliev papers, do not provide sufficient reasons to doubt the statements by Applicants that PRO274 has utility, and as previously discussed, the law does not require the existence of a "necessary" correlation between mRNA and protein levels, nor does the law require that protein levels be "accurately predicted." Applicants submit that according to the authors themselves, the data in the above cited references confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and show that a positive correlation exists between mRNA and protein. Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited reference and application of an improper, heightened legal standard. Applicants submit that they have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft et al., Hyman et al., and Pollack et al., (made of record in Applicants' Response filed September 14, 2004) collectively teach that in general, gene amplification increases mRNA expression. Second, the Declaration of Dr. Paul Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, shows that, in general, there is a correlation between mRNA levels and polypeptide levels.

Applicants assert that the Examiner appears to require Applicants to provide every single experimental detail involved in the testing of the mRNA/protein correlation according to the Polakis Declaration, and that such a requirement is unreasonable because neither the law nor the Utility Guidelines requires Applicants to do so. Regarding that Dr. Polakis is employed by the assignee, Applicants submit that note the sworn Declaration of Dr. Polakis is sufficient to support Applicants' position a general mRNA/protein correlation, even if Dr. Polakis is an employee of the assignee. Applicants submit that based on the above arguments, Applicants have clearly demonstrated a credible, specific and substantial asserted utility for the PRO274 polypeptide and the claimed antibodies that bind them, for example, as diagnostic markers for lung tumors.

Applicants' arguments have been addressed in the instant and previous office actions, and the Examiner maintains her position.

It is believed that all pertinent arguments have been answered.

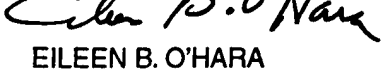
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nichol can be reached at (571) 272-0835.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.
Patent Examiner



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